where the sequencing, comparing and determination of a measure of phylogenetic relatedness are carried out.

37. The method of claim 1, wherein the infection control information is provided over a computer network.

Remarks:

Claims 1 and 3-37 are now pending in this application. Applicant have canceled claim 2, amended claims 1, 3, 4, 6, 8, 11, 12, 16, 17, 19, 21-28, 30, 32, and 33, and presented new claims 34-37 to clarify the present invention. Applicants respectfully request favorable reconsideration of this application.

Applicants submit herewith under separate cover selected sheets of new drawings to address the issues raised in the Notice of Draftperson's Patent Drawing Review.

The Examiner rejected claims 1-33 under 35 U.S.C. § 112, first paragraph. In particular, the Examiner objects to the recitation of the term "real-time" in the claims. The Examiner also asserts that utilizing the present invention on organisms other than *S. aureus* would require undue experimentation. Furthermore, the Examiner contends that the specification does not define infection risk factor determination. Additionally, the Examiner believes that the specification fails to provide sufficient guidance regarding generating costs.

Applicants assert that one skilled in the art would understand the meaning and that the specification provides an adequate description of "real-time". Along these lines, The McGraw-Hill Encyclopedia of Electronics and Computers (2d ed. 1988) provides the following definition for "real-time systems":

> Computer systems in which the computer is required to perform its tasks within the time restraints of some process or simultaneously with the system it is assisting. Usually the computer must operate faster than the system assisted in order to be ready to intervene appropriately.

Additionally, this references defines "Real-time control and real-time process control" as follows:

> In these applications the computer is required to process systems data (inputs) from sensors for the purpose of monitoring and computing system control parameters (outputs) required for the correct operation of a system or process. The type of monitoring and control functions provided by the computer for subsystem units ranges over a wide variety of tasks, such as turn-on and turn-off signals to switches; feedback signals to controllers (such as motors, servos, and potentiometers to provide adjustments or corrections; steering signals; alarms; monitoring, evaluation, supervision, and management calculations; error detection, and out-of-tolerance and critical parameter detection operations; and processing of displays and outputs.

As described in the Applicant's specification, the system of the present invention operates in "real time" because it can receive a stream of data (i.e DNA sequence data), analyze the data, and send infection control information *rapidly enough to allow infection control actions to be taken to control the spread of the outbreak.* The capability to provide rapid execution is a significant advantage of the present invention. Known methods analyze the spread of an outbreak after the outbreak has already finished. The lengthy time it takes to accurately genetically type an organism using prior art methods, such as Pulsed Field Gel Electrophoresis (PFGE) do not allow for real-time infection control. As described in the attached paper by de Lencastre et al., PFGE is a technique that can take 4-5 days or more. This is much longer than the technique of the present invention.

A significant advantage of the present invention is that it can provide infection control information before an infection has spread too far. For example, the system of the present invention could be used to prevent the spread of an infection outside of the burn ward of a hospital – or even outside of a particular room. Once the infection gets outside the hospital, it may be difficult to control. Therefore, providing infection control information rapidly is important. Alternatively, the system of the present invention could be used to prevent an infection from spreading outside of a hospital.

The system of the present invention can perform infection control procedures in real-time based on data as it is received and accumulated, while the outbreak is still occurring and while there is enough time to control the spread of the outbreak. Existing methods of hospital infection

control do *not* accumulate data and make decisions based on the collection of data while the outbreak is occurring and while there is time to control the spread of the outbreak. Existing methods such as PFGE take so long to perform, and are so difficult to compare objectively, that their results are not used to make infection control decisions in "real-time". For instance, by the time the result of a PFGE test is presented, a patient may have been discharged from the hospital, may have been relocated, or may have even died.

The real-time aspect of the invention is described in the specification. For example, at pages 5-6 of the specification in the Background of the Invention describes how PFGE and MLST typing methods are laborious and time consuming and thus "unsuitable for rapid infection control." In contrast, as described at page 7 of the specification, according to the real-time method of the present invention, microorganisms are sampled, sequenced, and analyzed, and then infection control information is transmitted "thereby allowing the health care facility to use the infection control information to control or prevent the spread of an infection."

In view of the above, one of ordinary skill in the art would understand that "real-time" means that the system operates rapidly enough so that it can provide infection control information while there is still time to control the spread of the outbreak.

With respect to applying the method of the present invention to other organisms, the specification fully enables one of ordinary skill in the art to make and use the claimed real-time invention without undue experimentation. For example, at page 18, the specification describes how to choose a gene with a good "clock speed" to allow for real-time infection control. At page

24, the specification describes how the server recognizes a potential outbreak and provides a warning to the hospital in real-time. Furthermore, at pages 25-30, the specification explains how to make a phylogenetic relatedness determination in real-time.

Once aware of the procedures of the present invention, it follows that the present invention can be used for other microorganisms other than *S. aureus* without undue experimentation. The procedures for analyzing phylogenetic relatedness for real-time infection control are explained in the specification at pages 25-32. Although the procedures are described in the specification with respect to the protein A gene (spa) or coagulase (coa) gene regions of the *S. aureus*, the same procedures for sequencing and analyzing sequences can be used to analyze the phylogenetic relatedness of other genes and other microorganisms. The described methods do not need to be modified to be applied to other genes or other microorganisms. Thus, the use of the claimed method can be applied to any gene of any microorganism without undue experimentation.

With respect to determining an infection risk factor, Applicants submit that the specification clearly describes the process for clearly describes how this determination is carried out. For example, at pages 14-15, the specification states

> The medical history will include factors that will determine the risk level of the patient for carrying a particular microorganism. For example, the patient can be asked whether he or she has been hospitalized recently, for how long, what kind of procedure, what foreign countries he or she has visited, etc. After obtaining the

answers to these questions, the risk level of the patient for carrying a potentially infectious agent can be determined.

Thus, the specification clearly states that the infection risk factor is based on information in the patient's medical history.

Still further, Applicants submit that the specification clearly provides guidance to one of ordinary skill in the art for generating relative cost, absolute cost, repeat motif cost, point mutation cost, and total cost. Along these lines, the specification states at page 26 that, "The relative cost is a measure of phylogenetic relatedness or phylogenetic distance between the two sequences being compared." Additionally, at page 28, the specification describes that insertion or deletion of a single A, G, C, or T in the sequence constitutes a single point mutation event. The specification even provides an example of an equation for calculating cost at pages 28-29. In this example, the Relatedness R is the cost; i.e. the measure of the relatedness between the two sequences being compared.

Additionally, techniques for measuring phylogenetic distance between sequences (i.e. cost) are known in the art. Applicants have attached an excerpt from the following three texts that describe techniques for measuring phylogenetic costs or edit distances. BIOLOGICAL SEQUENCE ANALYSIS, PROBABILISTIC MODELS OF PROTEINS AND NUCLEIC ACIDS, R. Durbin et al. (1998); TIME WARPS, STRING EDITS, AND MACROMOLECULES, THE THEORY AND PRACTICE OF SEQUENCE COMPARISON, Sankoff et al. (1999); and ALGORITHMS ON STRINGS, TREES, AND SEQUENCES:

COMPUTER SCIENCE AND COMPUTATIONAL BIOLOGY, Gusfield (1997).

In view of the above, Applicants submit that the claims are supported by an enabling specification and therefore comply with 35 U.S.C. § 112, first paragraph. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

The Examiner rejected claims 1-33 under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants have amended the claims to clarify the present invention. For example, Applicants have amended the claims to ensure that antecedent basis exists for all terms. In some cases, Applicants respectfully disagree with the rejection.

The specification, claims, and common knowledge provide sufficient clarity to the term "real-time", as discussed above. Also, one of ordinary skill in the art would understand the term "historical"" could include any data received and stored up to the present. This is explained on page 21 of the specification as follows: "The historical DNA is simply all of the previous isolate sequences that have been sent to server 118 and stored in centralized database 128."

The word "centralized" has been deleted from claim 28 to eliminate this confusion.

Regarding the recitation of "obtaining a sample of a microorganism", one of ordinary skill in the art would understand the term simply means obtaining one or more cells and/or one or more portions of a cell of a microorganism. The method of the present invention is not

limited as to the source of the microorganism. For example, claim 1 is not limited to a microorganism taken from a human nor is it limited to a microorganism taken from a kidney dialysis machine. The fact that claims 1, 32, and 33 are not limited as to the source of the microorganism does not make them vague and indefinite.

Regarding the lack of "requirement that the sample must be one containing an infectious agent, as described in the specification, not every microorganism sample taken from a patient will contain an infectious agent. The claimed method can be performed on perfectly healthy patients. In reality, humans may carry *S. aureus* naturally in their noses and not have an infection. Similar to the *E. coli* example described by the Examiner stated, *S. aureus* MAY BE naturally within the body of the patient and not infectious. In this example, a *S. aureus* is said to be colonized.

This makes the present invention even more important, because it is very possible that a person who carries *S. aureus* naturally in his or her nose may be the vector that infects other people, including the ability to infect him or herself. The ability of the present invention to type *S. aureus* and other organisms from a "non-infectious" person is a significant advantage. For example, the present invention can potentially identify vectors even if the human vectors are not infectious themselves.

Often, a healthcare worker becomes colonized through contact with a patient. That healthcare worker might then infect other patients. There are topical antibiotics that can be used to kill colonized bacteria. However, because of the fear of the bacteria becoming resistant to the

topical medicines, it is important that the medicines are only prescribed when necessary. The fact that the claim is not limited to samples with infected agents does not make the claims vague and indefinite.

Concerning the location where the determination of phylogenetic relatedness occurs, the present invention is not limited as to the location of where determination of phylogenetic relatedness occurs. As described in the specification, the determination of the phylogenetic relatedness can occur at infection control facility 148. The fact that claim 1 does not recite where the determination step occurs does not make claim 1 vague and indefinite.

With respect to the correlation between the phylogenetic relatedness determination and the infection control information, if the sample being analyzed is not an infectious organism, infection control information may or may not be sent. For example, a message reporting that the sample was not infectious would constitute infection control information. This would be understood by one of ordinary skill in the art. This does not make the claims vague and indefinite.

Applicants have amended claim 26 to clarify that the drug resistance and treatment information is a form of infection control information.

Applicants have amended claims 16, 17 and 19 so that the claims uniformly recite "phylogenetic relatedness", which is synonymous with "phylogenetic distance".

Regarding the locations of the database and the infection control facility, the specification at pages 16-17 explains that the remote facility, such as a hospital, can sequence the microorganism sample and transmit the sequence data to an infection control facility 148. Alternatively, the samples can be sent to the infection control facility 148 for sequencing. The present invention is not restricted as to the location of where sequencing occurs and the claims are broad enough to reflect this.

Applicants also submit that the claims are sufficiently definite with respect to the database location. While claim 4 recites the location of the database, it does not recite the location of where the phylogenetic relatedness determination occurs. Even if the phylogenetic relatedness determination occurs at the remote facility, the infection control information can still be provided to the remote control facility. For example, the infection control information could be provided by displaying the information on a computer screen or printing out a report.

Applicants have clarified the language of claim 5. Also, the term "suitably fast" is described in detail at page 18 of the specification. In this passage, the specification describes how to choose a gene with a good "clock speed" to allow for real-time infection control. While the term "suitably fast" may be a relative term, this does not mean that the term is vague or indefinite. As described in the specification, for a fast occurring outbreak, the mutation rate of the chosen region must be higher than for a slower occurring outbreak. Thus, the specification provides enough guidance to one of skill in the art to understand how fast the gene must mutate to provide real-time infection control.

Applicants amended the dependency of claim 6. Applicants have also amended the claims to address the Examiner's objection to the use of the term "health care facility".

Regarding the infection risk factor determination, the requirement that a microorganism sample be an infectious isolate and infectious state of a patient, the present invention does not require that the microorganism sample be an infectious isolate. For example, page 15 of the specification explains that a sample can be taken from patients who are determined to have a high risk of infection. Taking a sample from a patient is an example of "appropriate infection control measures" as recited in claim 10. Therefore, claim 10 is not vague or indefinite.

"Sensitive patient information" is adequately described at page 21 of the specification. Along these lines, the specification states, "In order to protect a patient's privacy, the health care facility does not need to send sensitive patient information such as the patient's name and social security number." Thus, one of ordinary skill in the art would understand "sensitive patient information" to mean information related to a patient's privacy that a patient would not want to make public. Therefore, claim 11 is not vague or indefinite.

Contrary to the Examiner's assertions, claim does recite a final process step that agrees back with the preamble. Along these lines, the specification describes at pages 8-9 that cost is a measure of phylogenetic relatedness. This is supported by the attached textbook excerpts regarding costs. Therefore, calculating a cost is a method of determining phylogenetic relatedness and claim 15 is not indefinite.

Applicants have clarified the language of claims 21, 22 and 24-27.

In view of the above, Applicants submit that all pending claims comply with 35 U.S.C. § 112, second paragraph, and respectfully request withdrawal of this rejection.

The present invention as recited in amended independent claim 1 includes a method of performing real-time infection control. The method includes obtaining a sample of a microorganism. A first region of a nucleic acid from the microorganism sample is sequenced. The first sequenced region is compared with historical sequence data stored in a database. A measure of phylogenetic relatedness is determined between the first sequenced region of the microorganism sample and the historical sequence data stored in the database based upon differences between the first sequenced region of the microorganism and the historical sequence data. Infection control information is provided based on the phylogenetic relatedness determination. The infection control information is utilized in the real-time control or prevention of the spread of an infection.

The Examiner rejected claims 1-4, 9, 12, 21, 25-27, 32 and 33 under 35 U.S.C. 102(a) as anticipated by Shopsin et al. (J. Clin. Microbiol., 1999). The Examiner rejected claims 1-4, 9, 12, 21, 25-27, 32 and 33 under 35 U.S.C. 102(b) as anticipated by Levitt (Emerg. Infect. Dis., 1998). The Examiner rejected claims 1-7, 9, 12-14, 21, 25-29, 32 and 33 under 35 U.S.C. 103(a) as unpatentable over Levitt, in view of Frenay et al (Eur. J. Clin. Microbiol. Infect. Dis., 1996) and Hoe et al (Emerg. Infect. Dis., 1999). The Examiner rejected claims 1-14, 21, 22-29, 32 and 33 under 35 U.S.C. 103(a) as unpatentable over Levitt, Frenay et al., Hoe et al., in further view

of O'Brien et al. (CHEST, 1997) and U.S. Patent 5,396,227 Carroll et al. The Examiner rejected claims 1-14, 21, 22-29, 32 and 33 under 35 U.S.C. 103(a) as unpatentable over Shopsin et al. (J. Clin. Microbiol., 1999) in view of O'Brien et al. (CHEST, 1997) and U.S. Patent 5,396,227 Carroll et al.

The Shopsin article represents the work of the inventors of the present invention. The other authors of this article, Shopsin, Gomez, Montogomery, Smith, Waddington, Dodge, Bost, and Riehman, performed work at the direction of one or both of the inventors. Typically, many people who contribute to an article, even in an editorial capacity, can be listed as an author. The standards for authorship and inventorship differ. The other authors of the Shopsin article are not inventors of the present invention, and thus not listed as inventors. Therefore, present invention was not described in a printed publication in this or a foreign country before the present inventors invented it. As a result, the rejections based upon the Shopsin article should be withdrawn.

Levitt does not disclose the present invention since, among other things, Levitt does not disclose a method of performing *real-time* infection control. Also, Levitt does not disclose a step of providing infection control information to control or prevent the spread of an infection. Rather, Levitt discloses a system that tracks the spread of an outbreak after the outbreak has already completely spread. In contrast, the present invention provides infection control information in real-time to prevent or control the spread of an outbreak.

Additionally, Levitt does not disclose steps of sequencing a first region of a nucleic acid

from a microorganism sample, comparing the first sequenced region with historical sequence data stored in a database, and determining a measure of phylogenetic relatedness between the first sequenced region of the microorganism sample and the historical sequence data stored in the database. Rather, Levitt discloses the use of phage typing and pulsed field gel electrophoresis. As explained in the Background of the Invention, PFGE is too slow and the comparison of results too subjective to be used for a method of real-time infection control.

While Levitt does state that "an electronic database at CDC will . . . include DNA patterns of foodborne pathogenic bacteria and epidemiological information associated with these isolates," the term "DNA patterns" refers to the patterns formed by PFGE tests, and not DNA sequence data. PFGE *is* a genetic typing test and the resulting patterns are based on the organisms DNA.

Levitt describes the PulseNet system. Applicants have attached a description of PulseNet obtained from the http://www.cdc.gov/pulsenet. This description confirms that that the "DNA patterns" used by PulseNet are PFGE images, not DNA sequence data.

In view of the above, Levitt does not disclose all elements of the present invention as recited in claims 1 and 3-39. Since Levitt does not disclose all elements recited in claims 1 and 3-39, the present invention, as recited in claims 1 and 3-39, is not properly rejected under 35 U.S.C. § 102(b). For an anticipation rejection under 35 U.S.C. § 102(b) no difference may exist between the claimed invention and the reference disclosure. *See Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 U.S.P.Q. 841 (C.A.F.C. 1984).

Along these lines, anticipation requires the disclosure, in a cited reference, of each and every recitation, as set forth in the claims. *See Hodosh v. Block Drug Co.*, 229 U.S.P.Q. 182 (Fed. Cir. 1986); *Titanium Metals Corp. v. Banner*, 227 U.S.P.Q. 773 (Fed. Cir. 1985); *Orthokinetics, Inc. v. Safety Travel Chairs*, Inc., 1 U.S.P.Q.2d 1081 (Fed. Cir. 1986); and *Akzo N.V. v. U.S. International Trade Commissioner*, 1 U.S.P.Q.2d 1081 (Fed. Cir. 1986).

Levitt does not suggest the present invention for the same reasons discussed above. Combining Levitt with Frenay et al. does not suggest the present invention since, among other things, Frenay also does not suggest a method of real-time infection control. While Frenay may suggest utilizing Spa typing as a method to identify outbreaks, Frenay does not suggest a method of performing real-time infection control based on DNA sequencing. Significantly, Frenay suggests *Spa* typing and does not suggest applied infection control. Neither Levitt nor Frenay suggests the use of DNA typing as a basis for infection control actions. Hoe et al. also does not suggest DNA typing as a basis for infection control actions.

Combining Levitt, Frenay et al., and Hoe et al. with O'Brien and Carroll does not suggest the present invention since, among other things, neither O'Brien et al. nor Carroll et al. suggests suggest DNA typing as a basis for infection control actions. O'Brien et al. only suggests monitoring patient compliance, not infection identification, prevention and control. Additionally, Carroll et al. only suggests an electronic monitoring system. This system in no way overcomes the deficiencies of Levitt, Frenay et al., or Hoe et al.

In view of the above, the reference relied upon in the Office Action does not disclose or suggest patentable features of the present invention. Therefore, the present invention is not anticipated by or obvious in view of the reference relied upon in the Office Action. Accordingly, Applicants respectfully request withdrawal of the rejections based upon the cited reference.

In conclusion, Applicants respectfully request favorable reconsideration of this case and early issuance of the Notice of Allowance.

In the event that the Examiner believes that an interview would serve to facilitate the prosecution of this application, Applicants respectfully urge the Examiner to contact the undersigned at the telephone number listed below.

The undersigned hereby authorizes the Commissioner to charge any insufficient fees or credit any overpayment associated with this communication to deposit account no. 19-5127, Order # 19124.0002.

Respectfully submitted,

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